

**REMARKS****Amendments to the Specification**

The specification has been amended to indicate that the parent application, 09/852,967, is now abandoned. No new matter has been added.

**Amendments to the Claims**

The Claims have been amended to recite "bipolar disorder" rather than "neuropsychiatric disorder." The Claims have also been amended to recite "two or more" instead of "one or more" nucleotide positions in the dopamine beta-hydroxylase gene. The Claims have also been amended to recite individuals who are symptomatic and/or at risk for development of bipolar disorder. New Claims 28-40 have been added. Support for Claims 28-36 can be found throughout the Specification, for example, at page 9, lines 3-22. Support for Claims 37-40 can be found throughout the Specification, for example, at page 9, lines 3-22 and Figure 2. No new matter has been added.

**Rejection of Claims 1-14 Under 35 U.S.C. § 112, First Paragraph**

Claims 1 to 14 are rejected under 35 U.S.C. § 112, first paragraph. The Examiner states that while the specification is enabling for methods for determining whether an individual has an increased likelihood of having or developing bipolar disorder, it does not reasonably enable any person skilled in the art to which it pertains to use the invention to diagnose any neuropsychiatric disorder. Claims 4, 5, 9, 13 and 14 have been canceled. The remaining claims have been amended to recite "bipolar disorder" rather than a "neuropsychiatric disorder."

The Examiner also states that the specification does not provide any information on the transmission of each of the alleles individually to affected offspring or on the transmission of 2 alleles to offspring; instead, the Examiner contends the specification only provides information on the transmission of the full haplotype of 3 polymorphisms. Applicants respectfully direct the Examiner to Figure 2 of the application, which provides transmission/association data for each of

the disclosed SNPs individually and pairwise in addition to the full haplotype of 3 S. Finally, the Examiner states that the specification does not provide any information on the general occurrence of the haplotypes of individual alleles in the general population versus an affected population and that there are no teachings in the specification as to how to apply the claimed method to the general population. The Examiner also notes that according to Cubells, there is significant heterogeneity in the frequency of the alleles across populations, demonstrating "the importance of controlling for population stratification in future studies testing for associations between DBH\*304S and clinical phenotypes."

Although the reference alleles do occur most frequently in the general population, the specification notes preferred instances in which the invention may be practiced, for example when couples are making reproductive decisions, to confirm a diagnosis of bipolar disorder, or in the assessment of individuals having a family history of bipolar disorder. In addition, the experimental method disclosed in the application of comparing those parental alleles transmitted to the proband to those not transmitted is called a transmission/disequilibrium test (TDT), which is used to overcome population stratification and is robust to non-random mating (Kirov, *Molecular Psychiatry* (1999) 4:558-565). Thus, the experimental findings demonstrating an association between a particular DBH haplotype with bipolar disorder should overcome any unpredictability in the art resulting from the heterogeneity of allele frequency. Notwithstanding this, Applicants have amended the claims to recite individuals who are symptomatic and/or at risk for the development of bipolar disorder.

Accordingly, with amendments made herein and as discussed above, it is respectfully submitted that the invention as claimed is fully enabled. Reconsideration and withdrawal of the rejection are respectfully requested.

Rejection of Claims 1, 2, 4, 6, 7, 10, 11, and 13 Under U.S.C. § 103(a)

Claims 1, 2, 4, 6, 7, 10, 11 and 13 are rejected under U.S.C. § 103(a) as being unpatentable over Cubells (Molecular Psychiatry (January 2000) 5:56-63; V). The Examiner states that Cubells teaches methods for detecting the presence of DBH\*444A and DBH\*5- del alleles which are associated with the occurrence of paranoia in cocaine-dependent subjects. The Examiner reasons it would have been obvious to one of ordinary skill in the art at the time of invention to use the method of Cubells to detect DBH\*444A and DBH\*5- del alleles for the diagnosis of cocaine-induced paranoia in order to rapidly identify cocaine-dependent individuals susceptible to the development of psychotic symptoms. The Examiner notes that the claims are inclusive of methods to detect DBH\*444A together with another allele and of methods that diagnose an increased likelihood of having any neuropsychiatric disorder, including addictive disorders, which encompass cocaine-dependent paranoia.

Applicants note that the claims have been amended to recite "bipolar disorder" rather than neuropsychiatric disorder. Cubells does not contain any teaching or suggestion related to an association with one of the disclosed polymorphisms and bipolar disorder. Reconsideration and withdrawal of the rejection are respectfully requested.

CONCLUSION

In view of the above amendments and remarks, it is believed that all claims are in condition for allowance, and it is respectfully requested that the application be passed to issue. If the Examiner feels that a telephone conference would expedite prosecution of this case, the Examiner is invited to call the undersigned.

Respectfully submitted,

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